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EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
04/23/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DocketDept@uspatent.com

Office Action Summary	Application No.	Applicant(s)	
	09/852,958	SIRBASKU, DAVID A.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-38,41-44,95-98,110-114 and 123-146* is/are pending in the application.

4a) Of the above claim(s) *44,96,98,133-135 and 137-146* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-38,42,43,95,97, 110,111,113,114,123-132 and 136* is/are rejected.

7)☒ Claim(s) *41 and 112* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/22/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/5/10 has been entered.

2. Claims 34-38, 41-44, 95-98, 110-114 and 123-146 are all the pending claims for this application.

3. Claims 34, 43, 95, 123-129 and 131 were amended and new Claims 137-146 were added in the Response of 4/5/10.

4. Newly submitted claims 137-146 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The elected and examined invention is directed to in vitro assay methods for detecting cancer cell growth stimulation of steroid hormone-responsive mucosal epithelial cancer cells by a substance of interest. The new claimed method is drawn to in vitro assay methods for detecting cancer cell growth stimulation of thyroid hormone-responsive mucosal epithelial cancer cells by a substance of interest.

The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually

exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed require different reagents used in the method steps and are directed to a different population of interest with different intended outcomes. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 137-146 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

5. Claims 44, 96, 98, 133-135 and 137-146 are withdrawn from examination.

6. Claims 34-38, 41-43, 95, 97, 110-114, 123-132 and 136 are the pending claims under examination.

7. This Office Action contains new grounds for rejection.

Information Disclosure Statement

8. The IDS of 2/22/10 has been considered and entered. The initialed and signed 1449 form is attached.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, first paragraph

Enablement

9. The rejection of Claims 34-38, 41-43, 95, 110-114 and 123-136 under 35 USC 112, first paragraph, because the specification does not reasonably provide enablement for a method of detecting steroid hormone-like cancer growth stimulation by a substance of interest for just cancer cell population is withdrawn.

The specification demonstrates IgA and IgM provide negative regulation of steroid hormone responsive *mucosal epithelial* cancer cell growth (p. 15, para 0030). In the most preferred embodiments, the inhibitors is/are dimeric IgA (non-sIgA) and polymeric IgM (p. 16, para 0032). The specification exemplifies the chemical and immunological properties of the partially purified CA-PS-pool II of steroid hormone reversible inhibitors of cancer cell growth wherein the long sought after serum-borne cancer cell growth inhibitors were found to include at least IgA and IgM in Example 20, p. 124-129. The only mucosal epithelial cancers tested in vitro for the dimeric IgA and/or the polymeric IgM inhibiting effect on steroid-hormone growth promotion on the cancer cells: MTW9/PL2 rat mammary cells, GH4C1, GH1 and GH3 rat pituitary cells, ZR-75-1 human breast cancer cells, MCF-7A and MCF-7K human breast cancer cells, T47D human breast cancer cells, H-301 Syrian hamster kidney cells, LNCaP human prostate cancer cells, and HT-29 human colon cancer cells (Ex. 21).

Applicants have amended the claims in the Response of 4/5/10 to recite that the cancers are mucosal epithelial cancers.

Written Description

10. The rejection of Claims 34-38, 41-43, 95, 110-114 and 123-136 under 35 USC 112, first paragraph, for lack of written description support for the anti-steroid, secretory immunglobulins is withdrawn.

The Examiner has established an evidentiary basis to support the conclusion that dimeric IgA (non-sIgA) and polymeric IgM are inhibitory for steroid hormone-induced cell proliferation of mucosal epithelial cancers, and Applicants have amended the claims in the Response of 4/5/10 to recite this form of cancer.

Claim Rejections - 35 USC § 112, second paragraph

11. The rejection of Claims 124 and 127 for the recitation that "Thyroid hormones" are steroid hormones is withdrawn.

Applicants have amended the claims in the Response of 4/5/10 to delete the species for "Thyroid hormones".

12. The rejection of Claims 129 and 130 for the recitation "a steroid hormone-dependent cancer cell growth stimulating effect by said substance of interest" is withdrawn in view of the explanation provided on pp. 13-14 of the Response of 4/5/10.

13. The rejection of Claims 131 and 132 for the recitation "an estrogenic dependent cancer cell growth stimulating effect by said substance of interest" is withdrawn in view of the explanation provided on p. 14 of the Response of 4/5/10.

14. The rejection of Claims 133-135 for reciting the steps for making the steroid hormone-depleted serum when the elected invention is a screening method for a substance is moot in view of the withdrawal of the claims in the Response of 4/5/10.

15. The rejection of Claim 135 for reciting the trademark/trade name "XAD™" is moot in view of the withdrawal of the claim in the Response of 4/5/10.

16. The rejection of Claim 135 for reciting the term "substantially" in the phrase "a substantially steroid hormone-depleted serum" is moot in view of the withdrawal of the claim in the Response of 4/5/10.

Claim Rejections - 35 USC § 112, first paragraph

New Matter

17. The rejection of Claims 123, 125, 126, and 128 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because Claims 123, 125, 126, and 128 recite "MCF-K human breast cancer cells" is withdrawn.

Applicants have amended the claims in the Response of 4/5/10 to recite "MCF-7K."

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Biological Deposit

18. The rejection of claims 123, 125, 126, and 128 under 35 U.S.C. § 112, first paragraph, because it is unclear if a cell line for MTW9/PL2, MCF-7K, or H-301 having the exact physical and chemical identity is known and publicly available, or can be reproducibly isolated without undue experimentation is maintained.

The rejection for the species "MCF-7A" is withdrawn in view of Applicants comments on p. 15 of the Response of 4/5/10.

The species "MCF-7K" is joined under this rejection.

The rejection was set forth in the Office Action of 12/4/09 as follows:

"The examiner's search of the ATCC website for public deposits for any of these cell lines did not identify any matches (see attached search outputs). Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of the claimed cell line is an unpredictable event.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified

statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice."

Applicants allegations on pp. 15-16 of the Response of 4/5/10 have been considered and are not found persuasive.

A) Applicants allege "the cell line MCF-7K is available from the Karmanos Cancer Center, Cell Line Repository (KCC) as the MCF-7, the K appended to the name to indicate that the cells were obtained from the KCC."

Response to Arguments

The examiner's search of the Karmanos Cancer Center website using the search term "MCF-7" did not identify the cell line being deposited under conditions ensuring availability to the public much less that the facility falls under the definition of a depository under the terms of the Budapest Treaty. See attached search output.

See MPEP 2401 stating in part:

"The Treaty requires signatory countries, like the United States, to recognize a deposit with any depository which has been approved by the World Intellectual Property Organization (WIPO)."

See MPEP 2405 stating in part:

"37 CFR 1.803 indicates that a depository will be recognized as acceptable for the purposes of these regulations if it is either an International Depositary Authority (IDA) established under the Budapest Treaty, or if it is a depository recognized as suitable by the Commissioner. After the effective date of these regulations, a deposit of biological

material which is made in a depository which is not recognized as acceptable under this regulation will not be considered as satisfying the requirements of 35 U.S.C. 112. See Ex parte Humphreys, 24 USPQ2d 1255 (Bd. Pat. App. & Int. 1992). On the other hand, if a deposit is not required to satisfy the requirements of 35 U.S.C. 112, it is permissible to make reference to such a deposit even though it may not be in a depository or made under the conditions which are acceptable under these regulations. As new depositories are recognized as suitable by the Commissioner, their identity will be announced in the Official Gazette. An organization may be recognized as suitable by the Office if the procedure and conditions specified in 37 CFR 1.803(a)(2) and 37 CFR 1.803(b) are followed. Generally, it is not the intention of the Office to recognize as suitable any organization where the need for a suitable depository for patent purposes is being met by depositories recognized as IDAs under the Budapest Treaty. Suitability will be judged by the Commissioner, based on need and the information supplied by the organization seeking status, and information obtained from other sources that may be consulted."

B) Applicants allege the "Cell lines H-301 and MTW9/PL2 are available from the inventor's company and are thus readily available to the public and have been described in publications In Vitro Cell Dev Biol 24, 42-52 (1988) (MTW9/PL2) and Endocrinology 98, 1260-72 (1976) (H- 301) and are thus known. These cell lines have already been supplied to other researchers…"

Response to Arguments

Applicants allegations on p. 3 of the response of 11/25/08 have been considered and are not found persuasive. Applicants allege "A description of the Fab63 antibody, a fully human antibody fragment that recognizes the Her2/neu extracellular domain, was published in Belimezi et al., Cancer Immunol. Immunother. 55:1091 (2006) (Exhibit A). As the antibody has been described in a scientific publication, members of the public can obtain the antibody from the authors of the publication. Thus, the Fab63 antibody is known and readily available to the public and a biological deposit is unnecessary."

Response to Arguments

MPEP 2404.01 states in part:

"In an application where the invention required access to specific biological material, an applicant could show that the biological material is accessible because it is known and readily available to the public. The concepts of "known and readily available" are considered to reflect a level of public accessibility to a necessary component of an invention disclosure that is consistent with an ability to make and use the invention. To avoid the need for a deposit on this basis, the biological material must be both known and readily available - neither concept alone is sufficient. A material may be known in the sense that its existence has been published, but is not available to those who wish to obtain that particular known biological material. Likewise, a biological material may be available in the sense that those having possession of it would make it available upon request, but no one has been informed of its existence."
and

"There are many factors that may be used as indicia that a biological material is known and readily available to the public. Relevant factors include commercial availability, references to the biological material in printed publications, declarations of accessibility by those working in the field, evidence of predictable isolation techniques, or an existing deposit made in accordance with these rules. Each factor alone may or may not be sufficient to demonstrate that the biological material is known and readily available. *Those applicants that rely on evidence of accessibility other than a deposit take the risk that the patent may no longer be enforceable if the biological material necessary to satisfy the requirements of 35 U.S.C. 112 ceases to be accessible.*" [examiner's italics]

and

"The mere reference to a deposit or the biological material itself in any document or *publication does not necessarily mean that the deposited biological material is readily available*. Even a deposit made under the Budapest Treaty and referenced in a United States or foreign patent document would not necessarily meet the test for known and readily available unless the deposit was made under conditions that are consistent with those specified in these rules, including the provision that requires, with one possible exception (37 CFR 1.808(b)), that all restrictions on the accessibility be irrevocably removed by the applicant upon the granting of the patent. Ex parte Hildebrand, 15 USPQ2d 1662 (Bd. Pat. App. & Int. 1990)." [examiner's italics]

Applicants sole reliance on the reference articles and Applicants own laboratory as the source for the availability of the cell lines would not necessarily ensure compliance under *In re Metcalfe*, 410 F.2d 1378, 161 USPQ 789 (CCPA 1969) and MPEP 2404.01 where the biological material is required to be publicly available during the enforceable life of the patent.

The rejection is maintained.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

19. Claim 37 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claim 37 is indefinite for the recitation "wherein the nutrient medium further includes non-heat inactivated serum" because it is not clear whether applicants are claiming an inactivated serum obtained by any other means than heating, or simply untreated serum. Clarification is requested.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

20. Claims 34, 37, 38, 42, 43, 95, 97, 123-132 and 136 are rejected under 35 U.S.C. 103(a) as being unpatentable over Furuya et al (Cancer Research, December 1989, Vol. 49, pp. 6670-6674) in view of Hoffman ('The Biochemistry of Clinical Medicine', 1970, pages 48 and 55).

The interpretation of the claims is of record.

Furuya et al teach that estradiol can neutralize growth inhibition exerted by the ammonium sulfate treated fraction of bovine serum. Furuya et al teach that bovine serum albumin fraction V containing globulin remnants inhibited cell growth, but that globulin-free bovine serum albumin did not inhibit cell growth (abstract). One of skill in the art would reasonably conclude that serum globulins were potentially the cause of the growth inhibition which estradiol, at sufficiently high concentrations, could overcome. Furuya et al teach that the established human breast cancer cell lines of MCF-7, ZR-75-1 and T47D (page 6670, lines 1-5 under "Introduction"). Furuya et al teach the attempt to study specific growth inhibiting characteristics of a standard, purified amount of a

serum constituent as a putative serum-inhibition factor and to determine the genuine effects of exogenous estrogen and/or tamoxifen, including the dual effect of estrogen in the presence of the serum growth inhibitor and a direct mitogenic effect of estrogen, and the inhibition thereof by tamoxifen (page 6670, second column, first full paragraph). Furuya et al teach that low and high doses of tamoxifen exert estrogenic and antiestrogenic effects, respectively, on MCF-7 cells, and that growth inhibition by tamoxifen decreases with increasing concentration of sGF or DCFBS, relative to serum free AIT medium, which when combined with tamoxifen demonstrated a lethal effect on MCF-7 cells (page 6674, fist column). Furuya et al teach that the mechanism of said effect has not yet been elucidated. Furuya et al do not teach growth stimulation by estrogen in the presence of the serum inhibitor which is purified plasma IgA, or purified plasma IgM.

Hoffman et al teach the constituents of serum include IgM, IgG and IgA within the globulin fraction (page 48, figure 4B). Hoffman et al teach that the globulin fraction of serum is ~2.5 g/100 ml of serum and albumin makes up the majority of the remainder of the protein content of serum (page 55, table 10, values for "Normal").

It would have been prima facie obvious to test the inhibitory contribution of various serum globulin proteins, such as IgM, IA or IgG in order t identify the growth inhibitory factor in serum, and the factor responsible for inhibiting the toxic activity of tamoxifen on the human breast cancer cell lines of MCF-7, ZR-75-1 and T47D. One of skill in the art would have been motivated to do so in order to understand the mechanisms and possible in vivo confounding factors effecting the action of drugs such

as tamoxifen in vivo. It would have been further obvious to carry out the tests using various combinations of estrogen, tamoxifen and the putative serum inhibitory factors such as IgM, IgG or IgA in multiple samples in order to determine if a statistically significant variation between samples with differing constituents was occurring.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 34-38, 42, 43, 95, 110, 111, 113, 114, 123-132 and 136 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 98-109 of copending Application No. 09/852,547 (US 20020006630). Although the conflicting claims are not identical, they are not patentably

distinct from each other because the claims of '547 render obvious the instant pending

claims as follows:

98. A method to detect estrogenic activity of a substance of interest, the method comprising: adding an inhibitory amount of purified IgM to at least two samples of a maintained steroid hormone-responsive cancer cell population in a nutrient medium; adding an amount of the substance of interest to one of the cell samples to yield a test mixture; designating the cell sample without any added substance of interest as a control mixture; incubating the cell samples for a period of time under cell growth promoting conditions; measuring the cell population in the cell samples after the period of time; and detecting estrogenic activity of the substance of interest from increased cell population doublings in the cell sample treated with the substance of interest compared with the cell sample without any added substance of interest.

99. A method to detect estrogenic activity of a substance of interest, the method comprising: adding an inhibitory amount of purified IgA to at least two samples of a maintained steroid hormone-responsive cancer cell population in a nutrient medium; adding an amount of the substance of interest to one of the cell samples to yield a test mixture; designating the cell sample without any added substance of interest as a control mixture; incubating the cell samples for a period of time under cell growth promoting conditions; measuring the cell population in the cell samples after the period of time; and detecting estrogenic activity of the substance of interest from increased cell population doublings in the cell sample treated with the substance of interest compared with the cell sample without any added substance of interest.

100. A method to detect estrogenic activity of a substance of interest, the method comprising: adding an inhibitory amount of purified IgM to at least three samples of a maintained steroid hormone-responsive cancer cell population in a nutrient medium; adding an amount of the substance of interest to one of the cell samples to yield a test mixture; adding an amount of estrogen to one of the cell samples to yield a standard mixture; designating the cell sample without any added substance of interest as a control mixture; incubating the cell samples for a period of time under cell growth promoting conditions; measuring the cell population in the cell samples after the period of time; and detecting estrogenic activity of the substance of interest from a significant increase in cell population doublings in the test mixture and the standard mixture compared with the control mixture.

101. A method to detect estrogenic activity of a substance of interest, the method comprising: adding an inhibitory amount of purified IgA to at least three samples of a maintained steroid hormone-responsive cancer cell population in a nutrient medium; adding an amount of the substance of interest to one of the cell samples to yield a test mixture; adding an amount of estrogen to one of the cell samples to yield a positive control mixture; designating the cell sample without said substance of interest or

estrogen as a negative control mixture; incubating the cell samples for a period of time under cell growth promoting conditions; measuring the cell population in the cell samples after the period of time; and detecting estrogenic activity of the substance of interest from a significant increase in cell population doublings in the test mixture and the standard mixture compared with the control mixture.

102. The method of claim 95 wherein said cells are further selected from the group of cell lines consisting of T47D, MCF-7A, MCF-7K or ZR-75-1.

103. The method of claim 102 wherein said cells are from the T47D cell line.

104. The method of claim 102 wherein said cells are from the ZR-75-1 cell line.

105. The method of claim 102 wherein said cells are further selected from the group consisting of the MCF-7A and MCF-7K cell lines.

106. The method of claim 95 wherein said cells are from the MTW9/PL2 cell line.

107. The method of claim 95 wherein said cells are further selected from the group of cell lines consisting of GH1, GH3 and GH4C 1.

108. The method of claim 107 wherein said cells are from the GH4C 1 cell line.

109. The method of claim 95 wherein said cells are from the H-301 cell line.

The cell lines in the claims of '547 are mucosal epithelial cancer cells which read on the instant generic claims.

The specification of '547 teaches and defines "a nutrient medium" as follows (MPEP 804 "The specification can be used as a dictionary to learn the meaning of a term in the patent claims. *Toro Co. v. White Consul Indus. Inc.* 199 F.3d. 1295, 1299 (Fed. Cir. 1999)):

"a ferric ion-free, calcium ion-containing, serum-free nutrient medium" [0024];

"steroid hormone depleted serum" [0251];

"serum or plasma was not heat pre-treated, or heat inactivated prior to use" [0216];

"Fibronectin was used with DDM-2MF to promote cell attachment " [0416];

"The total concentration of transferrin in serum is about 3 mg/mL. Usually, two-thirds of the total is apotransferrin. This amount is more than adequate to chelate Fe (III) in culture medium [0232];

"The preferred thyroid hormone is T.sub.3 (3', 5-triidothyronine (FW 673)), purchased from Sigma as Catalog No. T2752). It is stored desiccated at -20.degree. C. To prepare stocks, 0.5 N NaOH was made by addition of 20 grams of pellets to one liter of water. Then, 67.3 mg of T.sub.3 was added. After dissolving the T.sub.3 with stirring for a few minutes, 25 mL of this stock was diluted up to 250 mL with water, for a final concentration of 0.05 N NaOH. This dilution was sterilized using the 0.2 .mu.m pore diameter filter. At this point, the final stock for storage was 10 .mu.M T.sub.3. Aliquots of this final stock are stored in polystyrene tubes at -20.degree. C. The second thyroid hormone, thyroxin (T.sub.4, sodium salt, pentahydrate FW 888.9), is prepared by the same procedure. For this stock solution, 88.9 mg of T.sub.4 are used. T.sub.4 is purchased from Sigma (Catalog No. T2501). T.sub.4 is used at 10 to 20 times higher concentrations than T.sub.3. Care is taken not to freeze-thaw these preparations. Thyroid hormones have a very broad range of metabolic and growth effects, and many different types of cells require thyroid hormones for growth in serum free culture. [0413]

The variations described next are applicable to the defined media in TABLE 6. Standard phenol red-containing Gibco-BRL D-MEM/F-12 is a preferred basal medium to which the defined media components are added. It contains 0.6 mM to 1.0 M CaCl.sub.2. D-MEM/F-12 can be purchased from Gibco-BRL in the liquid form or can be

prepared from the powder formulation using only highly purified water. Alternatively, another suitable basal medium could be used as long as it provides at least the required minimum amounts of necessary nutrients, vitamins and minerals to maintain cell viability of the desired cell line. The calcium concentration range preferred is 0.6 to 10 mM. Calcium stabilizes the inhibitor in cell culture without impairing cell growth. The human breast cancer cell medium, DDM-2MF, was a modification of the original DDM-2 medium (Danielpour D et al. (1988) In Vitro Cell Dev Biol 24, 42-52) and MOM-1 (Ogasawara M and Sirbasku D A (1988) In Vitro Cell Dev Biol 24, 911-920) and contained modified hormone concentrations, deferoxamine (DFX) and fibronectin. Aqueous salt solutions such as tissue culture medium contain hydrolytic polymeric forms of Fe (III) (Spiro T G et al. (1966) J Am Chem Soc 88, 2721-2726). DFX binds this form of Fe (III) with very high affinity (Schubert J (1964) In; Iron Metabolism: The Chemical Basis of Chelation, Springer, Berlin, pp 466-498). If not removed, Fe (III) inhibits hormone-responsive growth in serum-free defined medium (Sirbasku D A et al. (1991) Mol Cell Endocrinol 77, C47-C55; Sato H et al. (1992) Mol Cell Endocrinol 83, 239-251; Eby J E et al. (1993) J Cell Physiol 156, 588-600; Eby J E et al. (1992) Anal Biochem 203, 317-325). The preferred cell growth media for conducting cell growth assays are substantially devoid of unbound Fe (III), i.e., preferably containing less than 1 .mu.M Fe (III), and more preferably containing no more than about 0.15 .mu.M. In preferred growth assay systems described herein, which are substantially devoid of unbound Fe (III), the concentration of free, or active Fe (III) in the medium is less than a cell growth inhibiting amount. Fibronectin was used with DDM-2MF to promote cell

attachment. The 35-mm diameter assay dishes were pre-coated by incubation with the designated amount of fibronectin (TABLE 6) for 16 to 48 hours at 37.degree. C. in 2.0 mL of D-MEM/F-12. CAPM human prostatic cancer cell medium was developed to support the growth of tumor cells from this tissue. The composition of CAPM is described in TABLE 6. CAPM also supports the growth of the H301 Syrian hamster kidney tumor cells. DDM-2A, which is a modified form of DDM-2 (Danielpour D et al. (1988) In Vitro Cell Dev Biol 24, 42-52), was preferred for growing MTW9/PL2 cells. PCM-9 defined medium was developed for growing the rat pituitary cell lines. This medium differs from previous PCM formulations (Sirbasku D A et al. (1991) Mol Cell Endocrinol 77, C47-C55; Sato H et al. (1992) Mol Cell Endocrinol 83, 239-251; Eby J E et al. (1993) J Cell Physiol 156, 588-600; Eby J E et al. (1992) Anal Biochem 203, 317-325) in that DFX was substituted for apotransferrin and the triiodothyronine concentration was increased to 1.0 nM. Although DFX and apotransferrin (2 to 50 .mu.g/mL) are the preferred chelators based on their very high specificity and affinities for Fe (III), EDTA at 1 to 10 .mu.M or sodium citrate at 10 to 1000 .mu.M also effectively neutralize the cytotoxic effects of Fe (III) (Eby J E et al. (1993) J Cell Physiol 156, 588-600). Ascorbic acid (vitamin C) also chelates Fe (III), but is used less often because it is unstable in cell culture medium at 37.degree. C. in an oxygen environment in the presence of salts and metals in the medium. Also, at concentrations of 50 to 100 .mu.g/mL, apo-ovotransferrin and apo-lactoferrin also were effective Fe (III) chelators in serum-free defined medium (Eby J E et al. (1993) J Cell Physiol 156, 588-600). Although EGF, aFGF and insulin are the preferred growth factors, several other human

recombinant proteins are effective. They have either been purchased or obtained as gifts from Gibco-BRL, Sigma or IMCERA Bioproducts. Insulin-like growth factors I and II (IGF-I and IGF-II) can be used to replace insulin, transforming growth factor .alpha. (TGF.alpha.) replaces EGF, TGF.beta. as an inhibitory supplement, and basic fibroblast growth factor (bFGF) partially replaces aFGF. Insulin can be used to replaced IGF-I and IGF-II. All of these protein growth factors are dissolved under sterile conditions according to manufacturers' instructions and stored as indicated." [0416]; and

"estrogens, progesterone and androgens" [0274],

which reads on the nutrient medium of the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

22. No claims allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Primary Examiner, Art Unit 1643